REMARKS

Initially, Applicants note that the Examiner has failed to acknowledge Applicants' claim to priority and receipt of the certified copies of the priority document.

Hence, Applicants hereby request that the Examiner acknowledge Applicants' claim to priority and receipt of the certified copy of the priority document, which was filed on January 24, 2000.

Support for new Claims 40-50 can be found, *inter alia*, in cancelled Claims 22-24, 35 and 38-39, and in the examples and at page 5 of the present specification.

In paragraph 2, on page 2 of the Office Action, the Examiner rejects Claims 22-24, 35 and 38-39 under 35 U.S.C. § 112, first paragraph.

Specifically, the Examiner states that while work by Applicants and the post-filing art teach methods of administration of Rp-8-Br-cAMPS and Rp-8-Cl-cAMPS to purified T cells (and specifically to T cells from patients having AIDS, for instance), and the resulting increase in proliferation of T cells in culture upon such administration, the specification and the art do not teach administration of such compounds to whole organisms for the therapeutic purposes claimed. Hence, the Examiner contends that undue experimentation is required to practice the present invention.

For the following reasons, Applicants respectfully traverse the Examiner's rejection.

Applicants submit herewith the Declaration of Kjetil Taskén. This Declaration clearly demonstrates that the

claimed compositions work as taught in the present invention, i.e., such are useful for treating immunosuppressive diseases. In the Declaration, MAIDS mice, which have an immunosuppressive disorder, were used and found to exhibit enhanced T cell function upon treatment with a claimed cAMPS antagonist. These results clearly show *in vivo* effects. Further, the MAIDS mouse animal model is well-known to correlate to effects in humans and other animals. The Declaration also provides relevant *in vitro* results for other cAMP antagonists, and demonstrates that the claimed effect is found for the general class of compounds which are cAMP antagonists.

The Examiner is requested to note that new Claim 45 (which substantially corresponds to cancelled Claim 38) does not refer to any specific disease, and thus the rejection is clearly improper with respect to the same.

Accordingly, Applicants respectfully submit that the claims are enabled by the present specification, and thus request withdrawal of the Examiner's rejection.

In paragraph 4, on page 6 of the Office Action, the Examiner rejects Claims 22-24 and 35 under 35 U.S.C. § 102(b) as being anticipated by Gjertsen et al.

Specifically, the Examiner states that Gjertsen et al teaches a composition comprising a cAMP antagonist, such as a thio-substituted cAMP analog, e.g., Rp-8-Br-cAMPS and Rp-8-Cl-cAMPS.

For the following reasons, Applicants respectfully traverse the Examiner's rejection.

Gjertsen et al discloses compositions containing Rp-8-Br-cAMPS and Rp-8-Cl-cAMPS only for use in *in vitro* experiments. Thus, the compositions of Gjertsen et al are not "pharmaceutical" compositions, as claimed in the present application. That is, a pharmaceutical composition must be one which is at least suitable for use in a clinical setting. Gjertsen et al does not teach or suggest such a composition.

More specifically, on page 20600, Gjertsen et al teaches that the antagonist was obtained from BIOLOG Life Science Institute. Applicants have contacted this company and have confirmed that the compounds they supply are not suitable for pharmaceutical administration (see the attached Declaration of Hans-Gottfried Genieger).

Accordingly, Applicants respectfully submit that the present invention is not taught or suggested in Gjertsen et al, and thus request withdrawal of the Examiner's rejection.

Finally, attached to the Office Action is a Notice or Draftsperson's Patent Drawing Review wherein the draftsperson objects to the drawings filed October 18, 1999, and requests that formal drawings be submitted.

Once allowable subject matter has been indicated by the Examiner, Applicants will file formal drawings in order to obviate the objections.

In view of the cancellation of Claims 22-24, 35 and 38-39, the addition of new Claims 40-50 and the arguments set forth above, reexamination, reconsideration and allowance are respectfully requested.

The Examiner is invited to contact the undersigned at his Washington telephone number on any questions which might arise.

Respectfully submitted,

Gordon Kit
Registration No. 30,764

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Facsimile: (202) 293-7860

Date: June 19, 2002

A P P E N D I X

Marked-up Version of Changes

IN THE CLAIMS:

Claims 22-24, 35 and 38-39 are being cancelled.

New Claims 40-50 are being added.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of :
Kjetil TASKÉN et al. :
Serial No. 09/428,458 : Examiner: M. Schmidt
Filed: April 29, 1998 : Group Art Unit: 1635
For: USE OF :
IMMUNOMODULATING AGENTS :

DECLARATION

Commissioner of Patents
and Trademarks
Washington, D.C. 20231

I, Hans-Gottfried Genieser, a German citizen of BIOLOG Life Science Institute, Research Laboratory and Biochemicals, P.O.B. 107125, D-28071 Bremen, Germany declare as follows:

1. I am CEO and General Manager of BIOLOG GmbH. I have been asked to comment on the form in which our compounds Rp-8-Br-cAMPS and Rp-8-Cl-cAMPS were supplied to investigators, for example for the studies published by Gjertsen et al (J. Biol. Chem., 1995, 270, p20599-20607).

2. The compounds were supplied as pure chemical (>99% purity) lyophilized in small quantities. Specifically, no filler or buffer was added and no pharmaceutical composition was made. The compounds were not produced under GMP-standard and thus contain trace amount of other chemicals and are therefore not suitable for in vivo use. As a consequence our products are labelled "for research purposes only" and "intended only for in vitro and non-human in vivo laboratory applications". These compounds sold by us are therefore not pharmaceutical compositions.

3. I further declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true, and that these statements were made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section

1001 of Title 18 of the United States Codes, and that such wilful false statements may jeopardize the validity of the application and any patent issuing thereon.

06/13/02

Hans-Gottfried Ganiesser

Date

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of :
Kjetil TASKÉN et al. :
Serial No. 09/428,458 : Examiner: M. Schmidt
Filed: April 29, 1998 : Group Art Unit: 1635
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DECLARATION

Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Declaration considered 9/8/03 MMS

I, Kjetil Taskén, a Norwegian citizen of Bergersletta 20, N-1349 Rykkinn, Norway declare as follows:

1. I am an inventor on the present application. I have conducted experiments in my laboratory to demonstrate the efficacy of cAMP antagonists in treating immunosuppressive disorders. The experiments which have been conducted are described in the following paragraphs.

2. The following experiment was conducted to determine the bio-distribution of Rp-8-Br-cAMPS in the tissues of animals following subcutaneous administration.

3. Rp-8-Br-cAMPS sodium salt and Rp-8-Br-cAMPS free acid were lyophilised, prepared as powder and packed to pellets of 30 mg. Pellets were implanted subcutaneously in healthy mice (CONTROL) and mice 12 weeks post-infection with the murine retrovirus Rad-LS that produces murine acquired immunodeficiency syndrome (MAIDS). The mice were viable, tolerated the procedure and treatment well and no local or systemic toxic effects were observed. After one week, mice were sacrificed and liver, spleen, lymph nodes and blood plasma was obtained for assessment of the concentration of the compound in those samples.

4. Suitable sample preparation and HPLC methods were developed

for quantitative determination of Rp-8-Br-cAMPS in mice tissues and serum samples to allow evaluation of drug concentrations of *in vivo* experiments (BioLog GmbH, Bremen, Germany). Calibrations were performed with Rp-8-Br-cAMPS and 8-Br-cAMP. Both compounds gave sufficient linearity in the range between 0 ng/mL and 1000 ng/mL.

5. Each mice sample (1000µL) was transferred into a borosilicate micro mortar followed by addition of 250 µL water. After manual homogenisation and addition of 750 µL water the resulting suspension was transferred into 1,5 mL sarstedt-tubes with screw caps. After a minimum period of 4 hours at -70°C all samples were freeze-dried in a Speed-Vac under oil-pump vacuum overnight. The freeze-dried material was suspended in 1000 µL MeOH/H_2O (1:1; v:v) and placed for 15 minutes in an ultrasonic bath, followed by centrifugation for 15 minutes (Heraeus; Biofuge*primo*; 13000 rpm). 0.85 mL of the supernatant was loaded onto an anion exchanger SPE cartridge (Chromafix 400mg SB / Art-Nr.: 731835 / Machery-Nagel), washed twice with 2 mL of water and then eluted with 1 mL 0,6 M NaCl. The resulting solution was used directly for HPLC analysis. For complete loading 300 µL of the solution was applied to the 200 µL sample loop. This volume produced reproducible data during calibration of the HPLC method.

6. The results are shown in Table 1 which appears in Annex 1. The values given for the Rp-8-Br-cAMPS concentrations are the mean of duplicate or triplicate HPLC analyses. As is evident from the data, both formulations delivered the compound to plasma and relevant tissues such as spleen and lymph nodes.

7. The therapeutic effect of *in vivo* treatment of MAIDS mice with Rp-8-Br-cAMPS was also investigated.

8. Osmotic pumps (Alzet, 100 µl) with Rp-8-Br-cAMPS dissolved in PBS (release rate of 0.7 mg/animal/day) or phosphate buffered saline (PBS) were implanted subcutaneously on MAIDS mice (14 weeks post infection) and healthy mice for 14 days. Infected and healthy mice were treated with 30 mg/kg/day Rp-8-Br-cAMPS. No toxic effect of the compound was observed.

9. Subsequently, T cell proliferative responses were assessed *in vitro* in a mixed population of unsorted lymph node mononuclear cells from animals treated with Rp-8-Br-cAMPS and animals that received PBS, by [^{3}H]-thymidine incorporation. T cell activation was accomplished in all samples by cross-ligation of anti-CD3 (mAb 2C11; 4 µg/ml). Cells were cultured for 72 h during which [^{3}H]-thymidine was included for the last 4 hours.

10. Figure 1, which is presented in Annex 2, shows the effect of *in vivo* treatment with Rp-8-Br-cAMPS on T cell immune function of cells from mice with murine acquired immunodeficiency syndrome (MAIDS). Mean values ± standard error of the mean (s.e.m.) from each group is shown (n=3-5).

11. Figure 1 shows that when T cell immune function was assessed in crude lymph node cells from treated and control (PBS)-treated infected mice after 2 weeks of treatment, whereas PBS-treated, infected animals had anti-CD3 induced proliferation in the range of 300 cpm, infected mice that received Rp-8-Br-cAMPS for 14 days had T cell immune responses to anti-CD3 that were increased more than 3-fold. Thus, treatment with Rp-8-Br-cAMPS increased anti-CD3 stimulated proliferation of cells from MAIDS mice compared to that of MAIDS mice that received PBS and brought the level of immune response to levels comparable to those of cells from healthy mice that received pumps with PBS.

12. The above described experiments are testament to the *in vivo* effects of cAMPS antagonists on T cells and illustrate that *in vivo* administration enhances T cell immune function of immunosuppressed animals. Based on this animal model it is my opinion that similar enhancement of T cell function which is immunosuppressed in other animals, including humans, could be expected.

13. I have also conducted further experiments to confirm that similar effects may be expected when using other cAMPS antagonists. cAMP antagonists were tested on human T cells *ex vivo* for their ability to reverse the inhibitory effect of a fixed dose of cAMP agonist (which mimics the situation in HIV T cells) on T cell

function. The potency of the compounds relative to Rp-8-Br-cAMPS is illustrated in Table 2 in Annex 3 in which potency indicates th ability to reverse inhibition of T cell function. These results thus indicate that T cell activation is observed for the cAMP antagonist class of compounds and thus similar effects to those described above for Rp-8-Br-cAMPS may be expected *in vivo*.

14. I further declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true, and that these statements were made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Codes, and that such wilful false statements may jeopardize the validity of the application and any patent issuing thereon.

.....JUNE 13, 2002.....

Kjetil Taskén Date

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of :
Kjetil TASKÉN t al. :
Serial No. 09/428,458 : Examiner: M. Schmidt
Filed: April 29, 1998 : Group Art Unit: 1635
For: USE OF
IMMUNOMODULATING AGENTS

ANNEX 1

TABLE 1 : Biodistribution of Rp-8-Br-cAMPS after subcutaneous administration

AIDS MICE/Rp-8-Br-cAMPS (free Acid)		
	concentration	concentration
Liver	420 ng/g	0,941 µmol/kg
Spleen	750 ng/g	1,681 µmol/kg
Lymph Nodes	280 ng/g	0,628 µmol/kg
Serum	140 ng/mL	0,314 µmol/L

CONTROL MICE/Rp-8-Br-cAMPS (free Acid)		
	concentration	concentration
Liver	320 ng/g	0,717 µmol/kg
Spleen	860 ng/g	1,927 µmol/kg
Lymph Nodes	240 ng/g	0,538 µmol/kg
Serum	50 ng/mL	0,112 µmol/l

AIDS MICE/Rp-8-Br-cAMPS (Sodium Salt)		
	concentration	concentration
Liver	110 ng/g	0,247 µmol/kg
Spleen	90 ng/g	0,202 µmol/kg
Lymph Nodes	100 ng/g	0,224 µmol/kg
Serum	100 ng/mL	0,224 µmol/L

CONTROL/Rp-8-Br-cAMPS (Sodium salt)		
	concentration	concentration
Liver	50 ng/g	0,112 µmol/kg
Spleen	40 ng/g	0,09 µmol/kg
Lymph Nodes	n.d. (not detectable)	n.d.
Serum	90 ng/mL	0,202 µmol/L

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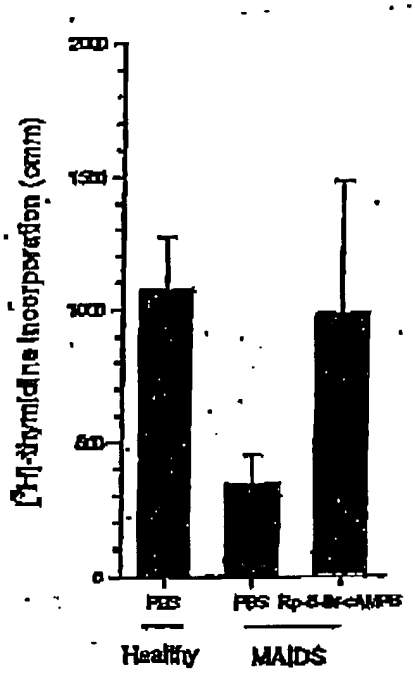
ANNEX 2

Figure 1


[3H]-thymidine incorporation (cpm)
2000
1500
1000
500
0
PBS
PBS Rp-8-Br-cAMPS
Healthy
MAIDS

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of :
Vidar TASKÉN et al. :
Serial No. 09/428,458 : Examiner: M. Schmidt
Filed: April 29, 1998 : Group Art Unit: 1635
For: USE OF
IMMUNOMODULATING AGENTS

ANNEX 3

TABLE 2 : Ability of cAMP antagonists to improve impaired T cell function in vitro

cAMP ANTAGONIST	POTENCY RELATIVE TO RP-8-BR-CAMPS
Rp-8-Br-cAMPS	1
Rp-8-Cl-cAMPS	0.78
Rp-8-Br-monobutyryl-cAMPS	0.52